ForPatients
by Roche

Metastatic Solid Tumors

A Phase I, Open-label, Non-randomized Study to Characterize the Impact of Dietary Modification on Inavolisib Associated Hyperglycemia and to Assess the CYP3A4 Induction Potential of Inavolisib using Midazolam as a Probe Substrate in Patients with Incurable Metastatic Solid Tumors Previously Treated with Multiple (#2) Lines of Therapy

Trial Status	Trial Runs In	Trial Identifier
Recruiting	2 Countries	GP43040

The source of the below information is the publicly available website ClinicalTrials.gov. It has been summarised and edited into simpler language.

Trial Summary:

A Study to Characterize the Impact of Dietary Modification on Inavolisib Associated Hyperglycaemia and to Assess the CYP3A4 Induction Potential of Inavolisib using Midazolam as a Probe Substrate in Participants with Incurable Metastatic Solid Tumours Previously Treated with Multiple (#2) Lines of Therapy

F. Hoffmann-La Roche Ltd Sponsor	**Phase 1** Phase

GP43040
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
Both	Above 18 years	No

Background and study aim:

Cancer is a disease in which abnormal cells divide without control and can invade nearby tissues. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) is a gene that controls a message telling cells to grow and multiply. This message is often involved in cancer when cells lose the ability to turn it off. This messaging system is called the PI3K cancer pathway. Inavolisib, the drug that is being studied, is designed to block

the wrong messaging from the mutated PIK3CA gene and, therefore, block the PI3K cancer pathway described above.

The main purpose of this study is:

1. To investigate the effect of dietary modification, in the form of a low carbohydrate diet, on inavolisib associated hyperglycaemia (high levels of glucose [sugar] in the blood) in high-risk participants (BMI (body mass index) # 30 and/or pre-diabetic) and low-risk participants (BMI < 30 and non-diabetic).

2. To determine the effect of morning (AM) dosing versus evening (PM) dosing of inavolisib in combination with a low carbohydrate diet on hyperglycaemia and changes in blood sugar levels in participants

3. To study the effect of multiple doses of inavolisib on how quickly and to what extent a dose of a mild sedative known as midazolam is absorbed and eliminated from the body, in Arm A

Who can participate?

People aged at least 18 years with PIK3CA-wild type or PIK3CA-mutated incurable metastatic solid tumours including breast cancer, endometrial cancer, ovarian cancer,head and neck squamous cell carcinoma, or colorectal cancer who have progressed after two or more prior lines of therapy.

What does the study involve?

The length of participation in the study depends on how long the participants continue to benefit from the treatment, which could range from one day up to a maximum of 2 years.

The study involves three parts:

1. Screening period of 21 days (to see if the participants are eligible for the study): The participants will be asked to complete some procedures and tests, including taking some blood and urine samples to check their eligibility. They might be asked to come back for further visits for confirmation.

2. Pre-treatment period of 6 days where participants will be started on a low carbohydrate diet.

3. Treatment Phase: The participants will receive the treatment drug(s) in 28-day cycles (each 28-day period is called a “cycle”). The participants will be expected to stay on a low carbohydrate diet in the first 3 cycles and thereafter it is recommended but not mandatory to follow the same.

During this study, the participants will be confined to the clinical research unit for a few days and will also have to make a few clinic visits on certain other days. The glucose (sugar) levels in the blood will be monitored via a continuous glucose monitoring device and participants will also be asked to attend regular radiographic tumour assessments (every 8 weeks) where images of the tumour will be recorded.

4. Follow-up (to check on the participant after treatment is finished): Following study treatment discontinuation, participants will be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the start of another anti-cancer therapy, whichever occurs first. There will be additional hyperglycaemia follow-up, if required, which will be monitored until resolution or for 90 days, whichever is sooner

Participants will be enrolled in two separate groups namely:

1. Arm A- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily either as morning or evening dose, starting on Day 2 of Cycle 1 through the discontinuation of study treatment. Participants will also receive midazolam syrup/solution, to be taken by mouth, once on Day 1 and 15 of Cycle 1.

2. Arm B1- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily either as morning or evening dose on Days 1-28 on each 28-day cycle.

3. Arm B2- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily as evening dose on Days 1-28 on each 28-day cycle.

The treatment will continue until the cancer worsens, the participants have medically unacceptable side effects, or if the participants decide to withdraw from the study.

What are the possible benefits and risks of participating?

Participants will not receive any direct medical benefit from participating in this study, but the information will other people who have a similar medical condition in the future. Participants may have side effects from the drugs or procedures used in this study that are mild to severe and even life-threatening, and they can vary from person to person. The very common side effects of inavolisib based on human and laboratory studies or knowledge of similar drugs, are listed below. There may be side effects that are not known at this time.

- Hyperglycaemia (increased blood sugar levels)
- Diarrhoea (loose stools)
- Decreased appetite
- Vomiting
- Nausea

- Dysgeusia/taste disorder (abnormal taste in mouth)
- Fatigue
- Alopecia (hair loss)
- Decreased weight
- Constipation
- Flatulence (gas)
- Rash
- Mucosal inflammation/stomatitis (inflammation of the lining of the mouth or ulcers of the lip or mouth)
- Asthenia (weakness)
- Headache
- Thrombocytopenia (low levels of cells called platelets)
- Hyponatremia (low sodium)
- Lymphopenia (low levels of a type of white blood cell)
- Eye inflammatory disorder (eye pain or sensitivity to light)
- Cataract (cloudiness of the eye)
- Colitis (inflammation [swelling and redness] of the large bowel [colon])
- Possible harm to a developing foetus, including birth defects and/or miscarriage
- Pneumonitis (inflammation of the lungs that may cause difficulty breathing and can be life threatening)
- Depressed immune function that may lead to increased risk of infections
- In males, reduced fertility or permanent sterility

Midazolam is a sedative drug and is used before surgical procedures. The following are the side effects:

- Tiredness, loss of memory, impaired attention, and impaired muscular function, which may adversely affect the ability to drive or use machines
- Some other “unknown” side effects include euphoria, depression, restlessness, drug dependence, drowsiness, headache, transient loss of memory, cardiac arrest, reduced respiratory rate, gastrointestinal disorders, skin reactions, weakness of muscles, tiredness, hypersensitivity.

There may be some risks associated with the procedures performed during the study:

- For blood samples - Discomfort due to swelling or bruising around the injection site, light-headedness, fainting (uncommon) and a small risk of infection at the injection site
- For electrocardiogram (ECG) - The sticky pads placed on the chest may cause skin irritation
- For magnetic resonance imaging (MRI) scans - If the participant doesn’t like confined spaces, it may make them feel uncomfortable being in the MRI scanner
- For computed tomography (CT) scans - A CT scan is a source of radiation exposure. Although the radiation that would be received is minimal it may increase the risk of cell changes in the body or having cancerous tumours. The radiation received in

this study is no more than the normal diagnosis and treatment of the illness and is not expected to greatly increase these risks, but the exact increase in such risks is unknown.

There may be a risk in exposing an unborn child to study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to study drug. If participants are pregnant, become pregnant, or are currently breastfeeding, participants cannot take part in this study.